Letters to the Editor

Methodologic Problems in the Assessment of Bleed Scores

Apostolakis et al. used the vitamin K antagonist (VKA) arm of the AMADEUS trial to assert the superiority of the HAS-BLED bleeding risk–prediction scheme over the $HEMORR_2HAGES$ and ATRIA schemes (1–4). Deficiencies in their study's design and analysis undermine this assertion.

First, their primary endpoint was clinically relevant bleeding (1) when the appropriate endpoint is major bleeding. The bleeding risk–prediction schemes, including HAS-BLED, were developed to predict major bleeding to help guide the anticoagulation decision in atrial fibrillation (AF). "Clinically relevant" bleeding is overwhelmingly composed of nonmajor bleeds. Although such events reduce patient persistence on anticoagulants, they are not comparable in impact to major bleeds and have little role in the anticoagulation decision. Trials of novel anticoagulant agents included nonmajor bleeds in their safety endpoint to increase the sensitivity of detecting a difference in bleeding risk versus VKAs, not because of the clinical importance of these events. When Apostolakis et al. restricted their analysis to major bleeding, the 3 schemes were similar in performance. Importantly, there were only 39 major bleeding events in the VKA arm. The authors do not report results from the idraparinux arm of the AMADEUS trial although there were 2.5 times as many major bleeds in that cohort (5). Precision is also a concern with the authors' assertion that the HAS-BLED scheme predicted intracranial hemorrhage. Few details of this analysis are provided. The AMADEUS trial reported only 9 intracranial hemorrhages in the VKA arm. Were the authors' analyses based on just 9 events?

HAS-BLED is distinctive in using "INR lability" as a predictor. There are strong arguments against including international normalized ratios (INRs) in bleeding risk–prediction schemes. First, there are no INRs available to the patient considering starting VKAs and, second, INRs are not applicable to novel anticoagulant agents. Furthermore, the use by Apostolakis et al. (1) of INRs likely biases the data in favor of the HAS-BLED score. For the $HEMORR_2HAGES$ and ATRIA scores, the authors include only baseline predictor values but for HAS-BLED, they include postbaseline information (i.e., INR values). Every variable included in HAS-BLED is included in the $HEMORR_2HAGES$ scheme except for INR lability. Presumably, this questionable use of postbaseline INR values accounts for the difference in performance between the 2 schemes.

The bleeding risk–prediction schemes are multipoint scores. A fair assessment would test the entire range of the point scores for each scheme both for c-indexes and for Cox models.

More generally, the bleed risk-prediction schemes were developed on AF cohorts in clinical care and meant to apply to patients in clinical care. Clinical trials generally exclude patients who have abnormal bleed score variables, thereby providing an inadequate test of score performance. Empirically, 77% of patients in AMADEUS had $HEMORR_2HAGES$ scores of ≤1, a markedly left-shifted distribution compared with the original $HEMORR_2HAGES$ cohort (3).

Although the AMADEUS trial is suboptimal for assessing bleed risk–prediction schemes, the authors could begin to address our concerns by assessing performance in both the idraparinux and VKA arms in AMADEUS, excluding INR values, including the entire range of point scores for each risk scheme, and restricting the endpoint to major hemorrhage.

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http://dx.doi.org/10.1016/j.jacc.2012.09.052

Please note: In the past 2 years, Dr. Singer has consulted for Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Johnson & Johnson, Merck, and Pfizer, manufacturers of antithrombotic agents, and for CSL Behring, manufacturer of blood products. In addition, Dr. Singer has received research support from the National Institutes of Health (National Institute on Aging and National Heart, Lung, and Blood Institute).

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The Analysis of Bleeding Risk–Prediction Scores Should Include All Major Bleeds

The study by Apostolakis et al. (1) compares the performance of bleeding risk–prediction scores in AMADEUS participants ran-